SYNTHESIS AND CURARIFORM ACTIVITY OF p,p''-BISQUATERNARY AMMONIUM DERIVATIVES OF p-TERPHENYL

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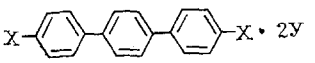
Work on synthetic replacements for d-turbocurarine has established several requirements for molecules of muscle relaxants. The majority of them are well known. Although numerous curariform compounds have by now been synthesized, there is still a great need for active preparations with high selectivity and various durations of action. Nondepolarizing agents are of greatest interest for medical use, since they should produce no side effects and have known antagonists.

Many years' work on various types of curariform compound in the Laboratory for the Synthesis of New Pharmaceuticals, Pharmacology Section, Scientific-Research Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, in conjunction with the Pharmacology Laboratory, I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Academy of Sciences of the USSR, have yielded a good number of suggestions regarding the correlation between structure and curariform activity. In particular it is thought that the structure of highly active nondepolarizing muscle relaxants should meet the following requirements: the presence of two quarternary ammonium groups in the molecule; the rigidity of the interquaternary chain; and the presence in the cationic heads of contacts that inhibit the conformational fluctuations of the choline receptor (I contacts).

In conformity with earlier suggestions [1], these requirements are met by the p,p''-bisquaternary ammonium derivatives of p-terphenyl with the general formula I:



I

X = $\overset{+}{N}R_2R'$, $\overset{+}{N}\langle\rangle(CH_2)_nR$

Y = $C_6H_5SO_3^-$, Hal^-

R and R' - alkyl, n = 4,5

The distance between the charged nitrogens is rigidly fixed at 14.4 Å. The cationic heads are bigger than trimethylammonium groups and are apparently capable of setting up the I contacts.

We synthesized these compounds by the reactions (see scheme on next page):

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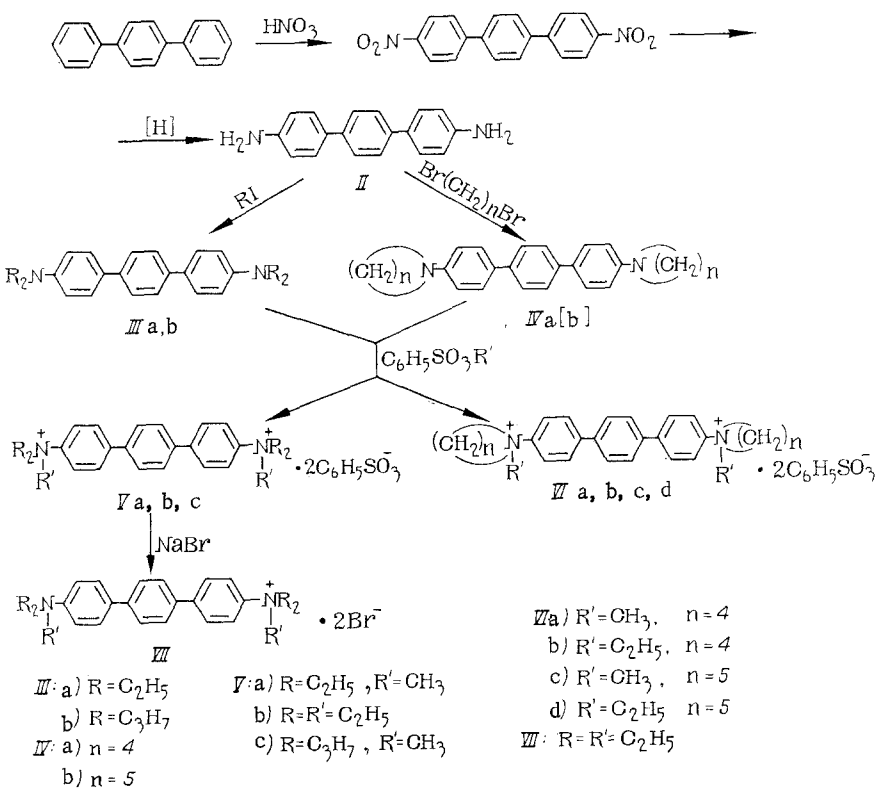

EXPERIMENTAL PHARMACOLOGY

We made a pharmacological study of the curariform effect of compounds of the general formula I in acute tests on cats (narcotized or decapitated), rabbits, mice, and pigeons, and in tests on isolated rat phrenic nerve—diaphragm preparation and isolated frog abdominal rectus muscle.

Our tests revealed that all these compounds are nondepolarizing muscle relaxants and that their effect is suppressed by cholinesterase inhibitors. Their neuromuscular blocking activity is similar to or greater than that of d-tubocurarine.

The fundamental properties of these compounds are summarized in Table 1 in comparison with d-tubocurarine.

Table 1 shows that the dibenzenesulfonate (Vb) and dibromide (VII) are most active. These compounds in the various specimens were four to eight times more potent than d-tubocurarine, while in contrast they have no histamine-releasing activity or ganglion-blocking effect on the autonomic nervous system, and consequently do not affect the arterial blood pressure. A weak and transient depressor effect develops in cats and rabbits only after a tenfold increase in the dose of these compounds. Conversely arterial pressure is markedly reduced after administration of one paralytic dose of d-tubocurarine. Moreover these compounds are nontoxic under conditions of artificial ventiliation. The animals survived administration of hundreds of blocking doses of these compounds, whereas d-tubocurarine caused death after no more than a five-to tenfold increase in the paralytic dose.

Experimental comparison of these compounds with the known nondepolarizing muscle relaxant pancuronium also reveals their superiority. Thus pancuronium in the paralytic dose causes elevation of pulse rate and arterial pressure, which is the cause of the intensified hemorrage in surgical procedures using pancuronium [2]. The tested compounds do not affect the arterial pressure in the paralytic dose.

A very significant advantage of these compounds over d-tubocurarine and pancuronium is the greater proserine antagonism. The clinical use of these compounds consequently provides safer and more controllable relaxation than when d-tubocurarine or pancuronium are used.

TABLE 1. Blocking Properties

Compound	Cats	Rabbits
	blocking dose, μmole/kg	dose inducing head drooping, mole/kg
Va	0,5±0,09	0,12±0,02
Vb	0,08±0,002	0,022±0,001
Vc	0,5±0,1	0,1±0,03
VIa	1,0±0,2	0,3±0,06
VIb	0,5±0,08	0,14±0,04
VIc	0,5±0,08	0,12±0,05
VId	0,3±0,04	0,1±0,03
VII	0,08±0,002	0,022±0,001
d-tubocurarine	0,5±0,02	0,18±0,06

CLINICAL

The most active of these compounds, (VII), which has been named tercuronium, has undergone successful clinical trials and has been recommended by the Pharmacological Committee for general medical use and commercial production. We present here the results of a clinical study of tercuronium.

The clinical trials of tercuronium in various surgical clinics included observations on more than 400 patients aged from nine to 70. We used the usual clinical tests and electromyography to evaluate the muscle-relaxing effect of the preparation. We also recorded the blood circulation indices, ECG, EEG, the gas composition of the blood, indices of acid–base equilibrium, and, in some patients, the blood potassium, histamine, and serotonin levels. In the majority of cases tercuronium was used as the major muscle relaxant to maintain relaxation after administration of compounds of the ditilin group or diadonium and intubation. Tercuronium was administered under these conditions in a dose of 0.08-0.15 mg/kg (5-10 mg per patient). The total muscle relaxation without active ventilation lasted from 20 to 60 min, depending on the dose and type of anesthesia. The equipotent dose on repeated administration was 0.04-0.07 mg/kg. Tercuronium was the sole relaxant in more than 40 surgical procedures and was also used in a dose of 0.16-0.3 mg/kg to facilitate intubation. After administration of the preparation in a dose of 0.3 mg/kg muscular relaxation, which allowed intubation to be carried out freely, developed after 80-90 sec, i.e., as rapidly as after the administration of compounds of the ditilin group in a dose of 1.5 mg/kg. The total muscular relaxation in this case lasted 2 h. After administration of the preparation in a dose of 0.16-0.2 mg/kg, better intubating conditions ensued from the start of the third minute. Electromyography showed that the amplitude of the muscle potential in this period was 35-40% of the control. The maximum effect (0-20% of the conductivity) developed after the eighth to eleventh minutes and persisted for 40-60 min. Emergence from the relaxed state was smooth and relatively rapid, taking 15-20 min. The comparatively brief period of return of muscle tone obviated the need for reversal in a considerable fraction of the patients, 60%; moreover the percentage of patients that did not require reversal rose with increasing experience in the use of tercuronium. If the preparation was the sole muscle relaxant or was used after intubation assisted by compounds of the titilin group, the residual relaxation could always be completely reversed by administration of the normal dose of proserine (0.02-0.03 mg/kg) or galanthamine. We found no cases of proserine-resistant relaxation. We should emphasize that proserine also has considerable deblocking potency in complete muscular relaxation and apnea induced by terconium. Repeated administration of proserine was required in some patients when tercuronium was administered after diadonium, used to facilitate intubation. Special investigation (V. L. Vanevskii) revealed that the effects of tercuronium were more efficiently reversed by the same dose of proserine in comparable groups of patients than were those of d-tubocurarine.

No important side effects were apparent under the conditions of the clinical use of tercuronium. A weak transient reduction in arterial pressure that required no treatment was detected in roughly half of the patients. Moderate dilation of the pupil sometimes occurred. A slightly elevated frequency and intensification of these side effects was discerned in patients who received tercuronium in conjunction with diadonium. In this case a

TABLE 2. Synthetic Conditions and Properties of (I)

Compound	Reaction temperature, °C	Reaction time, h	Melting point, °C	Yield, %	Found, %				Formula	Calculated, %			
					C	H	N	S		C	H	N	S
IIIa	120—130	2	198	70	83,42	8,61	7,61		$C_{26}H_{32}N_2$	83,82	8,65	7,52	
IIIb	100—120	2	115—6	70	84,03	9,57	6,98		$C_{30}H_{40}N_2$	84,06	9,40	6,53	
IVa	110—125	4	310	96	84,61	7,59	7,34		$C_{26}H_{28}N_2$	84,74	7,66	7,60	
IVb*	120—140	2											
Va	120	1	270,5	80	67,10	6,88	3,78	9,15	$C_{40}H_{48}N_2O_6S_2$	67,02	6,75	3,90	8,92
Vb	140	1	228—9 (decomposition)	70	67,97	7,66	3,80	8,55	$C_{42}H_{52}N_2O_6S_2$	67,72	7,04	3,76	8,59
Vc	120	1/4	245	80	66,39	7,43	3,59	8,24	$C_{44}H_{56}N_2O_6S_2 \cdot H_2O$	66,81	7,39	3,54	8,28
VIa	200	1/4	273—4	76	64,45	6,66	3,77	8,89	$C_{40}H_{44}N_2O_6S_2 \cdot H_2O$	64,15	6,46	3,74	8,55
VIb	200	1/6	277	80	66,50	6,70	3,65	8,43	$C_{42}H_{48}N_2O_6S_2 \cdot H_2O$	66,47	6,64	3,69	8,43
VIc	180	1/6	259—60	70	65,00	6,70	3,29	8,46	$C_{42}H_{48}N_2O_6S_2 \cdot 2H_2O$	64,93	6,74	3,60	8,23
VId	200	1/6	270	60	68,60	7,09	3,91	8,30	$C_{44}H_{52}N_2O_6S_2$	68,73	6,82	3,64	8,32

*Could not be isolated in the pure state.

slight increase or conversely a decrease in the pulse rate was also apparent in some of the patients. Several anesthesiologists consider that "in its properties tercuronium approaches the total nondepolarizing muscle relaxant; its effect develops rapidly and is easily controlled while its use in all stages of anesthesia and for the elimination of depolarizing relaxants from the practice of anesthiology..." (N. A. Osipova).

EXPERIMENTAL CHEMISTRY

The great virtue of p,p"-bisquaternary ammonium derivatives of p-terphenyl is that they can be simply and easily synthesized under commercial conditions from a readily available cheap starting material using common reagents and solvents.

The starting material for the synthesis is p-terphenyl, which is produced by Soviet industry. p,p"-Dinitro-p-terphenyl is periodically synthesized by the Shostka Plant of Chemical Reagents. However, we synthesized it by the literature method [3].

p,p"-Diamino-p-terphenyl (II). To a suspension of p,p"-dinitro-p-terphenyl (10 g) in ethylene glycol (500 ml) was added freshly prepared Raney nickel (5 ml) and then 99% hydrazine hydrate (15 ml) solution was carefully added dropwise with stirring and heating to 165-170°C. After 10-15 min activated carbon was added and the hot solution was filtered and cooled. The precipitate was washed on the filter with alcohol and dried to give (II) (8.1 g, quantitative yield), mp 240°C (literature [3] mp 241-242 °C).

p,p"-Bis(diethylamino)-p-terphenyl (IIIa). A suspension of (II) (8 g), calcium carbonate (10 g), DMF (100 ml), water (10 ml), and ethyl iodide (23 ml) was heated with vigorous stirring. The suspension was cooled and the precipitate was filtered and crystallized from DMF (100 ml) to give (IIIa) (7.65 g).

Compounds (IIIb), (IVa), and (IVb) were prepared under equivalent conditions. The reaction temperatures and times, constants, and yields, together with the analytical results for the synthetic compounds, are summarized in Table 2.

p,p"-Bis(triethylammonio)-p-terphenyl Dibenzenesulfonate (Vb). Compound (IIIa) (7.5 g) was heated with ethyl benzenesulfonate (20 ml). The solution formed in the first 30 min crystallized near the end of heating. After cooling the reaction mixture was treated with absolute ether and filtered. The precipitate was recrystallized from acetone—water (10:1) (100 ml) with activated carbon to give (Vb) (10 g). The product was dried under vacuum and stored in the dark.

Compounds (Va), (Vb), (Vc), (VIa), (VIb), (VIc), and (VId) were prepared under equivalent conditions. The reaction temperatures and times, constants, and yields, together with the analytical properties of the synthetic compounds, are summarized in Table 2.

p,p''-Bis(triethylammonio)-p-terphenyl (VII). Compound (Vb) (5 g) was dissolved in water (50 ml) with gentle warming and sodium bromide (7 g) was stirred in. The solution was left at room temperature for 12 h and then cooled. The resulting precipitate was filtered and crystallized from acetone–water (10:1) (100 ml) to give (VII) (4.2 g, 95%), decomposition point 195-197°C. The product was dried under vacuum and stored in the dark. Found, %: C 54.25; H 7.60; Br 23.90; N 4.29; $C_{30}H_{42}Br_2 \cdot 4H_2O$. Calculated, %: C 54.38; H 7.60; Br 24.12; N 4.23.

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ACID AND COMPLEX-FORMING PROPERTIES OF ANTIDIABETIC SULFONYLUREAS

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Recently the search for correlations between the physiological activity and physicochemical properties of compounds has attracted much attention [1, 2]. In particular there is information on the correlation between the complex-forming ability and antidiabetic activity of sulfonylureas (SU). However, this is sparse and contradictory, and the complexes were not qualitatively characterized [3, 4]. Here we report a study of the acid and complex-forming properties of antidiabetic SU's and their correlation with the type of substituent in the aromatic ring of the benzenesulfonamide fragment. We used Zn(II) as the complexing ion, since it is concentrated in the pancreas. The administration of SU's is known [5] to stimulate the release of zinc as well as insulin from the islets of Langerhans. This suggests that zinc is involved in the hypoglycemic effect of SU's.

EXPERIMENTAL METHOD

The materials used were: as a solvent, a mixture of ethyl alcohol and water (doubly distilled and freshly boiled); biologically active SU's (I)-(V), synthesized and purified by the method of [6]; zinc nitrate (pure for analysis grade), recrystallized twice; and potassium hydroxide (chemically pure grade). A solution of potassium hydroxide (about 0.1 M) in this solvent was prepared by the method of [7] and its exact concentration was established potentiometrically [8]. The zinc content (about 0.01 M) was determined by titration with trilon [9].

Studies were carried out by pH-potentiometry [10] using a pH-673 pH potentiometer (μ = 0.1) fitted with an ELS-43-07 glass electrode in the presence of $NACIO_4$, temperature 25.0 ± 0.2 °C. The calculations incorporated a correction for this solvent [11]. The zinc nitrate:SU concentration ratios were 1:1 and 1:2. The stability constants were calculated by Bjerrum's method [10] using the average ligand number n. The balance equations showed that zinc nitrate is completely dissociated and the concentration of its hydroxo complexes can be neglected in the experimental pH range (pH ≤ 6.0). All calculations were carried out with allowance for dilution. The dissociation constants pK_a of these SU's in this solvent, which were needed for the calculation of n, were also measured potentiometrically by the method of [10] within the limits of 20-80% neutralization.

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